REMARKS

These remarks are in response to the Office Action mailed February 22, 2008. Claim 42 has been canceled without prejudice to Applicants' right to prosecute the cancelled subject matter in any divisional, continuation, continuation-in-part or other application. Claims 41, 43, 66, 80-82, 87, 89, 91, 93, 95, 97, 100-105, 107-109, 111, 113, 119, and 121 have been amended. Support for the amendments can be found throughout the specification as filed (see, e.g., page 50, lines 8-10). No new matter is believed to have been introduced.

I. NON-STAUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 41-25, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, and 87-121 stand provisional rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 13-16, 19, 22, 223, 25 and 26 of copending application no. 11/805,411 (the '411 application) in view of both Yan *et al.* (Prostrate, 1997, 32:129-139) and Sobol *et al.* (U.S. Patent No. 5,674,486). Applicants respectfully traverse this rejection.

The rejection by the Office relies heavily on the primary reference being prior art. However, the '411 application is not prior art to the present application. Accordingly, the rejection is improper and may be withdrawn.

The '411 application's earliest priority date is November 24, 2004. The present application claims priority, as a continuation, to October 1, 1999, which claims priority to provisional application filed October 1, 1998 (more than 5 years prior to the '411 applications earliest priority date).

Accordingly, the Non-statutory Obviousness-type Double Patenting rejection is citing an application (the '411 application) as prior art, when in fact it is not. The policy behind a non-statutory obviousness rejection is to determine whether there is a time-wise extension of the claimed subject matter (*i.e.*, the subject matter claimed in the present application) compared to the cited reference (*i.e.*, the '411 application) (MPEP 804) that is an earlier application. As the Examiner will note there can be no time-wise extension of the present application beyond that of the '411 application. The present application, by statute (absent any patent term adjustments), will expire prior to the cited '411 application.

Furthermore, MPEP 804 indicates that the Examiner should apply a "one-way obviousness" test - this test is applicable when the *application being rejected is the later filed application* or both are filed on the same day. The test is applied based upon whether a claim pending in the "application at issue" would be anticipated by, or obvious in view of, an earlier filed application. This is the test that is being applied by the Office. The use of this test is in error in the present case. As noted above, the present application (*i.e.*, the application at issue) is the earlier filed application and thus this test does not apply.

Thus, the primary reference, the '411 application, is not prior art. Accordingly, the rejection should be withdrawn.

II. REJECTION UNDER 35 U.S.C. §103

Claims 41-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121 stands rejected under 35 U.S.C. §103 as allegedly unpatentable over Ram *et al.* (Cancer Research, 1993, 53:83-88) in view of each of Martuza et a. (U.S. Patent No. 5,585,096), Murakami *et al.*, (Gene, 1997, 202:23-29) and Sobol *et al.* (U.S. Patent No. 5,674,486). Applicants respectfully traverse this rejection.

As the U.S. Supreme Court stated in *KSR International Co. v. Teleflex Inc.* et al.:

> For over a half century, the Court has held that a "patent for a combination which ***only unites old elements with no change in their respective functions***…obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men."

U.S. Supreme Court No. 04-1350, Slip Op. at 11-12 (April 30, 2007) (emphasis added). As demonstrated below, Applicants' claimed invention is not a mere combination of old elements but a combination that results in a system that functions in a different manner resulting in unexpected genetic stability and usefulness of the RCR vectors. This type of advancement in the technology should be rewarded based upon the public policies of the Patent System.

Applicants through extensive experimentation and development demonstrate that not just any combination of elements (as suggested by the Office Action), not

just any insertion site (as suggested by the Office Action) and not just any viral vector (as suggested by the Office Action) would result in Applicants' claimed invention. Applicants were the first to discover that the combination of virus selection and IRES cassette insertion site provides a competent, stable and effective RCR system for treating cell proliferative disorders. For example, the Examiner is respectfully directed to Logg et al., J. of Virol., 75(15):6989-6998, 2001, which sets forth the importance of the cassette location. The combination of transduction efficiency, transgene stability and target selectivity was unknown in any recombinant replication competent mammalian oncoretrovirus prior the instant vector. The methods (and the vector composition used in the methods) provides insert stability and maintains transcription activity of the transgene and the translational viability of the encoded polypeptide.

The Office takes the position of dissecting out certain fragments of the invention then makes leaps to fill in the gaps on the development of Applicants' RCR vectors and methods using hindsight. The Office Action fails to appreciate that in 1998 (the priority date of the instant application), the state of the art was (i) replication *defective* vectors (Ram et al.), (ii) that replication competent vectors with transgenes were unstable, (iii) that vectors in use were incapable of mammalian infectivity (Murakami et al.) or (iv) were based on DNA viruses (Martuza et al.). Applicants' described inventions were a leap in technology recognized in numerous peered reviewed journals following Applicants' filing date.

As discussed more fully below, the varied and incomplete references (*e.g.*, a reference that teaches interferon is a useful cytokine), makes light of the advances provided by Applicants' claimed invention. It is not Applicants' position, for example, that the cytokine interferon is novel, but rather it is the viral vector, the methods, the stability of the viral vector and the use of the viral vector in treating cell proliferative diseases and disorders that is the "claimed invention".

To put the combination of the cited references in context and to demonstrate the lack of a prima facie case of obviousness each is described individually and then in combination. As will become apparent from the following remarks, the references either individually or in combination do not provide the necessary factors to set forth a *prima facie* case of obviousness.

As the Examiner indicates Ram *et al.* fail to teach or suggest a recombinant replication competent oncoretroviral vector or recombinant plasmid or recombinant polynucleotide encoding a replication competent oncoretroviral vector. Furthermore, Ram *et al.* fail to teach or suggest treating a tumor in the absence of a helper cell to assist in the defective viral replication, Ram et al. fails to teach or suggest a cytokine transgene, Ram et al. fails to teach or suggest a chimeric env protein, Ram et al. fails to teach or suggest a tissue specific promoter, and Ram et al. fails to teach or suggest an IRES cassette. Ram *et al.* is far removed from the methods and compositions of Applicants' invention, which utilize a replication competent, non-helper cell system to treat a cell proliferative disease or disorder.

The cited reference of Ram *et al.* describes a method that utilizes "retroviral producer cells" injected at the site of a tumor (see page 86, column 2, last paragraph of the cited reference). The producer cells support the *in situ* production of a retroviral vector containing a suicide gene. The producer cells are necessary because the vector is not replication competent. Further, the nucleic acid sequence encoding the suicide gene is located "just downstream of the 5' long terminal repeat sequence" (see page 84, column 1, lines 2-4 of the cited reference). It is clear from the contents of the cited reference that Ram fails to appreciate the significance of utilizing a replication competent oncoretrovirus in the absence of a producer cell to achieve efficient transduction. Because Ram et al. use a gutted vector, transcription of a transgene can easily be effected off the regulatory region of the 5'LTR. In contrast, Applicants' transgene is not directly linked to the 5'LTR. The location of the transgene and the preceding IRES as set forth in Applicants' claims is not insignificant.

Thus, Ram *et al.* is deficient in at least three aspects: (1) the vector is replication defective; (2) the methods require a help cell; and (3) the transgene location is of little or no important to Ram et al. The gutted size and location of the transgene in Ram et al. allow for the 5' LTR to serve as the regulatory region. To overcome these deficiencies the Office combines Ram *et al.* with Martuza *et al.*

The cited reference of Martuza *et al.* allegedly teach replication competent viral vectors derived from adenovirus and herpes simplex virus (such vectors are DNA vectors - very different than RNA vectors). Applicants respectfully submit this

is the first of many leaps the Office makes to overcome voids in the development of Applicants' claimed invention. First, it is not clear why one would combine a defective retrovirus with a DNA virus, the genomes are completely different. Nevertheless, when the references are combined the combination still fails to teach or suggest Applicants' claimed invention. Like Ram *et al.*, Martuza *et al.* fail to appreciate the importance of positioning a heterologous sequence encoding a therapeutic polypeptide in a region outside the LTR or not linked directly to the LTR of the viral vector. Nor do the combination of references teach, suggest, or appreciate an internal ribosome entry site. As will be recognized by the Examiner and those of skill in the art, merely inserting a transgene into a replication competent retrovirus does not provide a reasonable expectation that infectivity, stability or continued transmission and expression of the transgene will occur. In fact, numerous peer-reviewed journal articles indicate that insertion of transgene into U3 and other locations within a replication competent retrovirus can cause a loss of replication, and genetic instability of the vector (see, e.g., Logg *et al. supra*). Furthermore, the combination of Ram *et al.* with Martuza *et al.* do not teach or suggest the insertion of an IRES cassette into a replication competent retrovirus. Thus, the combination of Ram *et al.* and Martuza *et al.* fail to teach or suggest Applicants' claimed invention and do not provide any reasonable expectation of success in achieving a RCR having the transmission and genetic stability of Applicants' claimed vectors.

To overcome the deficiencies of Ram *et al.* and Martuza *et al.*, the Office combines Murakami *et al.*

Murakami *et al.* use a Rous Sarcoma Virus. The IRES-transgene insertions described in Murakami *et al.* consist of an IRES-transgene sequence positioned 3' to the env-encoding sequence and 5' to the 3' LTR. However, the cited reference utilizes replication competent avian sarcoma viruses (RCAS) which are distinct from the oncoretroviruses of the pending claims and incapable of replication in mammalian cells. Thus, the RSV vector could not be used to treat a mammal as set forth in Applicants' claims. The inability of RSV to produce infective viral particles in mammalian cells is disclosed in several peer-reviewed journal articles. Here, again, the Office makes a leap from a defective gutted retroviruses, to DNA viruses to avian

viruses, with little direction, suggestion or likelihood of success in the art. It is only through Applicants' disclosure and hindsight reconstruction that such very different viral architectures and functions can be pieced together. For example, the Office alleges that it would be a simple matter of substituting one viral type for another, however, this statement fails to address the many other factors which would lead one of skill in the art away from such combinations. For example, Avian Rous Sarcoma Virus naturally carries extra sequences (the src oncogene, which is in addition to the gag, pol and env genes required for replication, and which is similar in size to the env gene) positioned just after env. Thus, RSV evolved a capacity to incorporate a large piece of extra sequence in this location in its genome, something not found in mammalian oncoretroviruses. The idea of putting an IRES-transgene insert after the env gene in a mammalian oncoretrovirus would not be obvious in view of the cited references simply because there are no known naturally-evolved replication-competent mammalian oncoretroviruses with extra genes following the env (or anywhere else, for that matter). In fact, it was recognized in the art that inserting a transgene in the region following the env gene although providing short term expression ultimately resulted in genetic instability and loss of the transgene in subsequent rounds of replication. RSV through natural development has developed a "transgene insertion site" because it contained a non-essential and replaceable gene (src), thus providing additional flexibility compared to mammalian oncoretroviruses. One of skill in the art would have not recognized, prior to Applicants' invention, insertion of an IRES transgene cassette into a replication-competent MLV vector at the claimed location because MLV and other mammalian oncoretroviruses were known to not have such dispensible genes and therefore not have the same flexibility known to RSV. Simply put one of skill in the art would not have looked to MLV, for example, because there are not any parts of the MLV genome that are known to be dispensable.

Further, combining the IRES-transgene of Murakami *et al.* and the vector described by Martuza *et al.* would not result in a vector or method described or claimed in the instant application. It is not clear why or how one would combine a DNA viral vector and an RNA viral vector. Furthermore, there would be no reasonable expectation of success of merely inserting a sequence immediately

downstream of the *env* gene in an HSV genome without disruption of the viral life cycle.

Finally, the Office combines Sobol *et al.* with Ram *et al.*, Martuza *et al.*, and Murakami *et al.*, for the teaching of cytokines to treat cancer. The Office appears to be picking and choosing the use of certain reference and avoiding the teachings of the reference as a whole. When taken as a whole, Sobol *et al.* actually teach that one should avoid the use of replication competent retroviruses. For examples, Sobol *et al.* teach throughout the specification that one should use proper screening, production and removal of replication competent retroviruses from any system or method. Applicants respectfully submit that the Office appears to be viewing Sobol *et al.* with respect to only "certain" teachings in the reference and fail to recognize the more important teaching away of the reference in that one should avoid replication competent retroviruses. However, even in view of such a teaching away, Sobol *et al.* do not remedy the deficiencies as set forth above regarding the replication competent retrovirus and use of such recombinant viral vectors for the treatment of cell proliferative disorder.

Not only do the cited references when combined fail to identify predictable solutions for achieving a replication competent oncoretrovirus capable of delivering a therapeutic polypeptide to dividing cells, they also fail to provide all the components necessary for the production of the vector set forth in the claimed methods.

In contrast, the Applicants have succeeded in developing a replication competent oncoretroviral vector with an enhanced capability to stably deliver a heterologous sequence to a dividing mammalian cell. Once integrated into a target cell, the novel vector produces a therapeutic polypeptide encoded by the heterologous sequence. In addition, viral particles which infect neighboring dividing cells are also produced in the absence of helper cells.

It is important to understand that the surprising combination of transduction efficiency, transgene stability, and target selectivity provided by Applicants' inventions were simply unknown in any recombinant replication competent mammalian oncoretrovirus prior to the Applicants' invention. When placed in a mammalian oncoretroviral background, the cassette is useful for the stable expression of a transgene coding sequences including marker genes such as green

fluorescent protein (GFP), suicide genes such as thymidine kinase, cytosine deaminase (CD) or purine nucleoside phosphorylase (PNP), and genes encoding cytokines such as interferon.

For at least the foregoing reasons, the pending claims are novel and non-obvious over the cited reference. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claims 41-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105-107, 109, and 115-121 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ram *et al.* taken with each of Martuza *et al.*, Murakami *et al.* and Sobol *et al.* in further view of Douar *et al.* Applicants respectfully traverse this rejection.

The teachings of Ram *et al.* Martuza *et al.*, Murakami *et al.* and Sobol *et al.* are applied as above and are traversed as above.

Douar *et al.* do not overcome the deficiencies of the prior references (*i.e.*, Ram *et al.*, Martuza *et al.*, Murakami *et al.*, and Sobol *et al.*). At most Douar *et al.* teach that VSV-G pseudotype has a broader host range. This does little to assist the Office in overcoming the deficiencies of the other cited references (including deficiencies in the positioning, development of an IRES cassette in an RCR to infect mammalian cells).

Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 41-45, 49-51, 56, 58, 59, 61 66, 70, 71, 73, 75, 78-80, 87-92, 97-102, 105-110, 115-119, and 121 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ram *et al.* taken with each of Martuza *et al.*, Murakami *et al.* and Sobol *et al.* further in view of Vile *et al.* and Yan *et al.* Applicants respectfully traverse this rejection.

The teachings of Ram *et al.* Martuza *et al.*, Murakami *et al.* and Sobol *et al.* are applied as above and are traversed as above. None of these cited references teach or suggest tissue specific promoters. Vile *et al.* is combined for the alleged teaching of a retroviral vector comprising a tissue specific promoter. The retroviral vector use in Vile *et al.* lacks the env and is replication defective. Thus, there could

be no insertion of an IRES cassette 3' to the env gene or 5' to the 3' LTR as recited in Applicants' claims. The combination of reference thus fails to teach and suggest a replication competent retrovirus comprising and IRES cassette (optionally an cytokine transgene or suicide gene transgene; optionally a tissue specific promoter) capable of infecting and retaining stability and transmission in mammalian cells.

Ram *et al.*, Martuza *et al.*, Murakami *et al.*, Sobol *et al.*, and Vile *et al.* fail to teach or suggest a probasin promoter or a dual probasin promoter. To overcome this deficiency, the Office combines Yan *et al.* Yan *et al.* teach a probasin promoter. However, Yan *et al.* do not teach or suggest retroviral vectors and do not overcome the deficiencies of the prior references.

Furthermore, a publication by Logg *et al.* (J. of Virol., 76(24):12783-12791, 2002), that is not prior art to the present application, describes that the dual androgen response element promoter functions a 1000 fold better than the wild-type promoter. Such unexpected replication efficiency would not have been apparent to someone of skill in the art, further demonstrate the importance of the vectors and methods of the disclosure.

Claims 41-45, 49-51, 56, 58, 61, 63-73, 75, 78-82, 87-119, and 121 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ram *et al.* taken with each of Martuza *et al.*, Murakami *et al.*, Sobol *et al.* further in view of Kasahara *et al.* Applicants respectfully traverse this rejection.

The teachings of Ram *et al.*, Martuza *et al.*, Murakami *et al.* and Sobol *et al.* are applied as above and are traversed as above. None of these cited references teach or suggest tissue specific promoters or chimeric envelopes. Kasahara *et al.* is cited for the alleged teaching of chimeric envelopes.

Applicants respectfully submit that the mere piecing together of references fails to address the unexpected and novel properties of the claimed invention. It is the invention as a whole, not bits and pieces that should be examined. When the claimed invention is taken as a whole the novelty and non-obviousness, i.e., the "change in the respective function" (*KSR*, *supra*) of Applicants' invention are clear. None of the cited references demonstrate or provide a method of treating cell proliferative diseases and disorder using a replication competent retrovirus

comprising an IRES cassette and transgene in mammalian systems. The Kasahara *et al.* reference do not teach the IRES cassette as set forth in the methods of the claimed invention capable of infecting mammalian cells. Accordingly, Kasahara *et al.* in combination with any and all of the cited references fails to teach or suggest the claimed invention as a whole.

III. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, and 87-121 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. In particular, the Office Action alleges that the term, "at the 5' or 3' end" is new matter. Applicants respectfully traverse this rejection.

Applicants respectfully direct the Examiner to page 64, lines 16-20, which explains that the LTR need only be present at one or both of the 5' or 3' ends and that during reverse transcription the LTR is duplicated. Accordingly, delivery of a vector comprising a single LTR would be sufficiently duplicated during the RCR life cycle (see also page 67 and figure 8). Furthermore, page 18 and 19 explain the viral life cycle including that upon transcription the provirus "now" has two identical repeats at either end. Accordingly, Applicants submit that the disclosure includes support (including figurative support) for the recited phrase.

For, at least, the foregoing reasons the claims submitted herewith are non-obvious over the references either alone or in combination.

For at least the foregoing, the Applicant submits that the claimed invention is patentable and request reconsideration and notice of such allowable subject matter.

The Director is authorized to charge any required fee or credit any overpayment to Deposit Account Number 50-4586, please reference the attorney docket number above.

The Examiner is invited to contact the undersigned at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

GAVRILOVICH, DODD & LINDSEY LLP

Date: August 22, 2008

By: /Joseph R. Baker, Jr./
Joseph R. Baker, Jr.
Registration No. 40,900

4445 Eastgate Mall, Suite 200
San Diego, California 92121
(760) 479-0474